COR ET VASA 55 (2013) E309–E314

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/crvasa

Original Research Article — *Special issue: Heart Failure*

Prevalence of donor-transmitted atherosclerosis—Clinical utility of intracoronary ultrasound early after heart transplantation. A single-center study

Helena Bedanova[a,b,*], *Marek Orban*[a,b,1], *Martin Tretina*[a,1], *Ales Tomasek*[a,1], *Petr Malik*[a,1], *Petr Fila*[a,2], *Vladimir Horvath*[a,3], *Jiri Ondrasek*[a,3], *Radka Stepanova*[b,4], *Petr Nemec*[a,b,5]

[a]*Center of Cardiovascular and Transplant Surgery Brno, Pekarska 53, 65691 Brno, Czech Republic*
[b]*International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic*

ARTICLE INFO

Article history:
Received 20 December 2012
Received in revised form
15 March 2013
Accepted 21 March 2013
Available online 29 March 2013

Keywords:
Heart transplantation
Coronary allograft vasculopathy
Donor-transmitted coronary atherosclerosis

ABSTRACT

Introduction: Coronary allograft vasculopathy (CAV) is one of the main factors limiting long-term survival following orthotopic heart transplantation (HTx). Whether or not and, if so, how donor-transmitted atherosclerosis (DCA) affects the post-transplant course of the allograft recipient is still unclear. Conventional coronary angiography is a moderately accurate technique for DCA detection as it will reveal only the more gross morphological lesions. By contrast, intravascular ultrasound (IVUS) has been shown to be a much more sensitive technique for CAV and DCA detection. In our study we sought to determine the prevalence of DCA in our HTx patient population and identify main risk factors of DCA based on donor characteristics.

Patients and methods: We performed a retrospective analysis of data of 119 patients (92 men, 27 women) undergoing transplantation in our center from August 2006 through September 2012, who had survived their first post-transplant month and had coronary angiography and IVUS.

Results: DCA was present in 39 patients, and not documented in 80 patients. The main risk factors for DCA included donor age, cigarette smoking, and hypertension; the other parameters were not shown to be statistically significant. In-hospital mortality was low in both groups (DCA positive and DCA negative), with one patient dying in either group. One-year mortality rates post-HTx were likewise almost identical in both groups (15.4% and 15% in DCA positive and negative, respectively).

*Corresponding author at: Center of Cardiovascular and Transplant Surgery Brno, Pekarska 53, 65691 Brno, Czech Republic. Tel.: +420 543182521; fax: +420 543182541.

E-mail addresses: hbedanova@seznam.cz (H. Bedanova), maor@post.cz (M. Orban), martin.tretina@cktch.cz (M. Tretina), ales.tomasek@centrum.cz (A. Tomasek), malik.cktch@seznam.cz (P. Malik), petrfil@hotmail.com (P. Fila), vladimir.horvath@cktch.cz (V. Horvath), jiri.ondrasek@cktch.cz (J. Ondrasek), radka.stepanova@fnusa.cz (R. Stepanova), petr.nemec@cktch.cz (P. Nemec).

[1]Tel.: +420 543182531.
[2]Tel.: +420 543182517.
[3]Tel.: +420 543182495.
[4]Tel. +420 602565725.
[5]Tel.: +420 543182483.

http://dx.doi.org/10.1016/j.crvasa.2013.03.012

Conclusion: The prevalence of DCA in our patients was 32.8%, with major risk factors for DCA including donor age, cigarette smoking, and hypertension. As age seems to be the strongest predictor, coronary angiography should be a routine examination in individuals aged over 40 years; the examination should be considered in younger individuals with a cluster of several of risk factors. The 1-year survival in this selected patient population was identical in both groups, the implication being that the diagnosis of DCA had no effect on 1-year survival post-HTx.

1. Introduction

Heart transplantation still remains to be the method of choice in selected patients with end-stage heart failure. At present, survival half-life of patients post-HTx is longer than 11 years, with the main factor precluding longer survival being coronary allograft vasculopathy. The paucity of suitable younger donors makes us accept increasingly older donors more likely to have coronary atherosclerosis. According to the International Society of Heart and Lung Transplantation (ISHLT) registry, the mean age of donors is 40.2 years in Europe, and 31.6 years in North America. While, 5 years ago, individuals aged 50 made up only 20% of all donors, the figure was as high as 30% last year [1]. The mean age of donors in our center was 33 years 10 years ago, 38 years 5 years ago, 40 years last year, and as high as 45 years this year. These data clearly indicate that the prevalence of donor-transmitted atherosclerosis is going to increase. In his study, Tuzcu reported that atherosclerotic lesions in the coronary arteries are present in one in six teenagers. Judging by the above study, the prevalence of atherosclerosis could potentially vary between 17% in donors below 20 years of age and 85% in those aged over 50. Given the sedentary way of life, low physical activity, and obesity in children and young individuals, this trend is most unlikely to reverse [2]. Both the increasing donor mean age and the development of coronary atherosclerosis at an increasingly younger age as well as the fact that CAV continues to be the Achilles' heel in the field of heart transplantation led to the need for a proper definition of CAV and standardization of terms within this specialty. In addition to the established terms of IVUS-based classification of atherosclerosis (atheromas, calcifications, plaque and thrombi), several studies have shown association between maximal intimal thickness (MIT) of coronary arteries and adverse cardiovascular outcomes following HTx [3,4]. The cutoff value widely used is MIT $\geq$0.5 mm. In the ISHLT Consensus Statement on standardized nomenclature for cardiac allograft vasculopathy, the panel of experts admits that "IVUS-detected maximal intimal thickening may be most useful for its negative predictive value at any time after transplant; however, we do not see a role for routine IVUS surveillance. IVUS-defined intimal thickening is predictive of developing angiographic CAV and may guide treatment, but this remains speculative". Therefore we decided to conduct an observational study aimed at determining the relationship between angiographic and IVUS finding on coronary arteries early after HTx and long-term outcomes (angiographic and/or IVUS CAV, myocardial infarction and mortality). In this manuscript we present data on the prevalence of CAV related findings found shortly after HTx and compare the results with other studies.

2. Patient group and methods

A total of 150 heart transplantations in 118 men and 32 women were performed in our center between August 2006 and September 2012. We made a retrospective analysis of database data from 119 of our patients surviving the first post-transplant month and had coronary angiography and IVUS. Table 1 shows the basic characteristics of the patient population and Table 2 presents the basic characteristics of the respective graft donors.

3. Immunosuppression and endomyocardial biopsy

All patients were treated using an immunosuppressive protocol with a conventional triple combination of cyclosporine A (Sandimmunn Neoral, Novartis) or tacrolimus (Prograf, Advagraf, Astellas Pharma), mycophenolate mofetil (Cellcept, Roche), and corticosteroids. All patients received induction therapy with monoclonal antibodies, initially daclizumab (Zenapax, Roche) or basiliximab in the last 2 years (Simulect, Novartis). Endomyocardial biopsy was performed as per protocol once a week in the first month post-HTx and, subsequently, once a month until a total of 10 biopsies over the first post-transplant year. Histological findings were evaluated using the Banff classification.

4. Technique for intravascular ultrasound and measurement

Intravascular ultrasound (IVUS) was performed 3–4 weeks post-HTx. Following heparin administration, a 6F catheter was advanced into the left coronary artery using a guidewire. In patients 0.4 mg sublingual nitroglycerin was administered before advancing the IVUS catheter. Next, IVUS catheter (Volcano Eagle Eye Platinum) was inserted distally to the left anterior descending artery (LAD) over an ultrathin guidewire and pulled manually proximally from the distal segment of the artery. Patients with documented calcifications and/or atheromas within the visualized course of the artery were defined as a group with donor-transmitted atherosclerosis (DCA). Coronary atheromas and calcifications have been validated according to the ACC Clinical Expert Consensus published previously [5–7]. In patients without DCA, maximum intima–media thickness (MIT) was measured at two pre-defined sites, bifurcations of LAD and r. circumflex (RC),

Table 1 – Basic characteristics of recipients examined by ICUS.

Variable	Statistics	DCA positive N=39	DCA negative N=80	p*
Sex	N (%)	32 (82.1%)	60 (75.0%)	0.389
Male	N (%)	7 (17.9%)	20 (25.0%)	
Female				
Age (yrs)	Mean (SD)	50.7 (11.86)	50.6 (11.19)	0.823
	Median (Q1-Q3)	53.0 (43.0–61.0)	54.0 (43.0–59.5)	
	Min–Max	21–66	21–66	
Number of rejection episodes	N (%)	27 (69.2%)	50 (62.5%)	0.239
1	N (%)	8 (20.5%)	15 (18.8%)	
2	N (%)	2 (5.1%)	8 (10.0%)	
3	N (%)	–	5 (6.3%)	
4	N (%)	2 (5.1%)	2 (2.5%)	

SD=standard deviation, Q1=lower quartile, Q3=upper quartile.
* p value in the Mann–Whitney test for comparison of continuous variables between groups, or the chi-square test for comparison of categorical variables.

and LAD and r. diagonalis (RD1). Definition of sites of measurement is important for the follow-up analysis, which will be the subject of further investigation.

5. Statistical analysis

Basic characteristics of recipients and donors were presented using the methods of descriptive analysis. Results are given as mean with standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3), minimum and maximum with continuous variables, and using absolute and relative numbers with categorical variables.

The endpoints were compared between patients divided by DCA positivity or negativity. Categorical variables were compared using the chi-square test or, possibly, Fisher's test. As continuous variables do not show a normal distribution pattern, the non-parametric Mann–Whitney test was employed to compare inter-group parameters.

Any association between coronary heart disease and DCA incidence was determined using univariate and multivariate logistic regression models. Results are given as the odds ratio (OR) and its 95% confidence interval.

All analyses were conducted at a level of 5% significance (i.e., p values <0.05 are considered statistically significant).

6. Results

We reviewed data from 119 HTx patients from our database. Baseline demographic data of the recipients are shown in Table 1. There was no statistically significant difference in age, gender and rejections between subjects with and without documented DCA.

Based on IVUS findings acquired 3.4 ± 1.1 weeks after transplantation, we documented DCA in 39 (32.8%) patients with donor hearts. Out of 80 patients without documented IVUS signs of DCA, mean MIT was 0.44 ± 0.28 mm. When using the cutoff of 0.5 mm, 59 (74%) patients had MIT less than 0.5 mm.

Table 2 shows the association between the risk factors for coronary heart disease in donors and DCA. Using univariate logistic regression models, donor age, cigarette smoking and hypertension were identified as predictors of DCA incidence in our group of patients.

Multivariate logistic regression analysis identified donor age and the presence of at least another two risk factors for coronary heart disease (hypertension, smoking, diabetes mellitus, hyperlipoproteinemia, male sex, or obesity) as independent predictors of the DCA (Table 3). Based on the results of our study, donor age seems to be the most significant independent predictor of DCA. Age over 45 in men and 55 in women raises the odds ratio for having DCA by a factor of 6.5 when compared with younger donors (OR=6.48; 95% CI=2.638; 15.937). Presence of at least one of the above risk factors for coronary heart disease increases the odds for having DCA by a factor of 3.5 (OR=3.48; 95% CI=1.431; 8.504).

7. Discussion

Based on the analysis of single-center retrospectively collected data from 119 heart recipients, we found signs of DCA in one third of our HTx patient population. We have also identified a subgroup of patients with increased MIT as a surrogate of impaired outcome. When reviewing a rather limited body of evidence in the literature, we found very good agreement with data from other groups. Li et al. reported prevalence of donor lesions in 30% of HTx population [8]. In case we applied their definition of pre-existing donor lesions including MIT ≥0.5 mm, the prevalence of DCA would have been higher in our patient population. This finding can be explained by significant difference in donor population age in both studies (29.6 ± 12.7 vs. 42.1 ± 10.9 years). Furthermore, Konig et al. studied a total of 18 patients using IVUS including Virtual Histology and demonstrated donor transmitted coronary atherosclerosis in 33% [9].

Based on the results, we have clearly identified age, tobbaco abuse and hypertension as risk factors of DCA. Other conventional risk factors of CAD (diabetes, hyperlipoproteinemia, male

Table 2 – Basic characteristics of donors.

Variable	Statistics	DCA positive N=39	DCA negative N=80	p*
Sex	N (%)	32 (82.1%)	59 (73.8%)	0.316
Male	N (%)	7 (17.9%)	21 (26.2%)	
Female				
Age (yrs)	Mean (SD)	49.5 (6.72)	34.6 (12.39)	<0.001
	Median (Q1-Q3)	51.0 (45.0–54.0)	33.0 (23.0–45.5)	
	Min–Max	21–66	21–66	
Diabetes mellitus	N (%)	2 (5.1%)	1 (1.3%)	0.207
Yes	N (%)	26 (66.7%)	66 (82.5%)	
No	N (%)	11 (28.2%)	13 (16.2%)	
Unknown				
Hypertension	N (%)	14 (35.9%)	11 (13.8%)	0.005
Yes	N (%)	21 (53.8%)	60 (75.0%)	
No	N (%)	4 (10.3%)	9 (11.2%)	
Unknown				
Smoking	N (%)	13 (33.3%)	11 (13.8%)	0.017
Yes	N (%)	16 (41.0%)	44 (55.0%)	
No	N (%)	10 (25.6%)	25 (31.3%)	
Unknown				
Hyperlipoproteinemia	N (%)	3 (7.7%)	4 (5.0%)	0.368
Yes	N (%)	18 (46.2%)	56 (70.0%)	
No	N (%)	18 (46.2%)	20 (25.0%)	
Unknown				
Obesity[a]	N (%)	4 (10.3%)	6 (7.5%)	0.727
Yes	N (%)	35 (89.7%)	74 (92.5%)	
No	N (%)	–	–	
Unknown				
Total number of risk factors	N (%)	2 (5.1%)	15 (18.8%)	<0.001
0	N (%)	7 (17.9%)	36 (45.0%)	
1	N (%)	13 (33.3%)	19 (23.8%)	
2	N (%)	9 (23.1%)	8 (10.0%)	
3	N (%)	8 (20.5%)	2 (2.5%)	
4				

SD=standard deviation, Q1=lower quartile, Q3=upper quartile.
* p value in the Mann–Whitney test for comparison of continuous variables between groups, or the chi-square test for comparison of categorical variables.
[a] BMI > 30 kg/m^2.

gender or obesity) lacked statistical significance. This could be partly due to selection bias with lack of detailed data on personal history of donors. When adding a multivariate analysis, a cumulative effect of risk factors was found.

Donor hearts with DCA are more prone to acute graft failure immediately post-transplant, and may later progress more rapidly to CAV; both these conditions are the two most common causes of morbidity and mortality post-HTx [10–12]. To be able to determine whether the problem is not DCA but true CAV, it is critical to have adequate information about the actual status of donor coronary arteries. While a number of centers require coronary angiography prior to HTx in patients aged over 40, the examination is unavailable in some, and others do not insist on performing the examination. Moreover, coronary angiography provides just a quick look at coronary arteries and is definitely less accurate than IVUS. As reported by Tuzcu et al. [2], none of their donors below 30 years of age showed abnormal coronary angiograms, yet IVUS demonstrated atherosclerosis in 28% of them. Besides, given the scarcity of donors, insignificant lesions shown in donor coronary angiograms (stenoses <30%) do not pose a reason for disqualifying the graft. It is just the presence of these "insignificant narrowings" that may result in faster development of CAV. Whatever the case, knowledge of the patient's initial status in the early post-transplant period is the most important factor playing a pivotal role in their fate.

One of the first studies reporting on the association between the outcome of IVUS-based examination and post-HTx outcome was conducted by Mehra et al. [13] showing that patients with intimal thickening >0.5 mm experienced more myocardial infarctions, there were more deaths in their subgroup, and patients required more re-transplant procedures during a 4-year follow-up. Perhaps even more importantly, Rickenbacher reported an adverse effect of intimal thickening >0.3 mm [14]. Patients with these values were shown to have significantly worse 4-year survival rates (73% vs 96%). It was just the absence of IVUS assessment immediately post-transplant and, consequently, the inability to distinguish DCA from CAV that were the main limitations of Mehra et al.'s

Table 3 – Association between donor risk factors for coronary heart disease and incidence of DCA.

	OR (95% CI)	
Age[a]	7.54	(3.175; 17.920)
Hypertension	3.64	(1.430; 9.244)
Smoking	3.25	(1.212; 8.708)
Diabetes mellitus	5.08	(0.441; 58.420)
Hyperlipoproteinemia	2.33	(0.477; 11.423)
Male sex	1.63	(0.624; 4.238)
Obesity[b]	1.41	(0.374; 5.316)

OR = Odds ratio, CI = confidence interval.
[a] Age over 45 in males and 55 in females.
[b] BMI > 30 kg/m^2.

study who had otherwise demonstrated that the presence of the same intima–media thickness at 3 years post-HTx may, but need not, result in cardiac events occurring in these patients [15]. When evaluating the effect of the rate of intimal thickening progression on a patient's fate post-HTx, Kapadia noted that rapid intimal thickening progression (>0.5 mm) over the first post-transplant year increases the risk for serious cardiac events in that patient subgroup (myocardial infarction, death, heart failure) [16]. The authors of studies examining the effect of DCA on long-term survival post-transplant have reported inconsistent data. In their series of 301 patients, Li et al. documented a frequent incidence of DCA (in up to 30% of patients) yet found no effect of DCA on the rate of intimal thickening progression and survival of patients having HTx [8].

By contrast, Yamasaki, Gao, and Wong showed that the presence of donor-transmitted atherosclerotic plaques is associated with their more rapid progression and accelerates the rate of allograft vasculopathy post-HTx [10,11,17].

Coronary artery atherosclerosis in non-transplant patients is mostly due to dyslipidemia whose treatment, particularly with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), clearly improves the prognosis of these patients, prevents progression of atherosclerotic plaques while stabilizing them [18–20]. Statins have also been found beneficial in transplant recipients who often develop dyslipidemia. Hence, statins have become an integral part of therapeutic protocols perhaps in all centers performing heart transplantation. In these patients, statins reduce the risk for sudden death and incidence of severe acute cellular rejection episodes, and arrest or at least slow the development of CAV [21–24].

In their IVUS study, Wenke et al. even documented a reduction in MIT over the first post-transplant year in an average 50% of statin-treated recipients compared with those not receiving statins [25].

Potential pharmacological options in modulating and slowing the rate of DCA progression may include angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers and, in particular, TOR inhibitors (sirolimus, everolimus). An IVUS study by Mehra exploring the effect of ACE inhibitors and calcium-channel blockers reported that patients treated with some of these drug classes showed smaller intimal thickening compared with a control group [26].

Another possible approach is to modify the immunosuppressive protocol by instituting TOR inhibitors as soon as possible after transplantation. A number of studies demonstrated a significant antiproliferative potential of these agents in terms of reducing and slowing that rate of CAV progression and, consequently, improved long-term survival after heart transplantation [27–30].

Our study has several limitations. First is the retrospective design of the study. Second is the relatively small number of study subjects, but this is the major problem of most of the single center studies performed in HTx patients. It was also the main reason for a relatively long period of enrollment of the patients. Finally, Virtual Histology was not a part of IVUS examination, since this application has not been available for all exams.

8. Conclusion

The prevalence of DCA in our patients was almost 33%. The major risk factors implicated in donor DCA have been identified to be donor age, cigarette smoking, and hypertension. As age seems to be the strongest predictor, coronary angiography should be a routine examination in individuals aged over 40 years; the examination should be considered in younger individuals with a cluster of several risk factors.

Acknowledgment

The study was supported by the European Regional Development Fund—Project FNUSA-ICRC no. CZ.1.05/1.1.00/02.0123.

REFERENCES

[1] C. Benden, P. Aurora, L.B. Edwards, et al., The Registry of the International Society for Heart and Lung Transplantation: Fourteenth Pediatric Lung and Heart–Lung Transplantation Report—2011, Journal of Heart and Lung Transplantation 31 (10) (2012) 1045–1095.
[2] E.M. Tuzcu, S.R. Kapadia, E. Tutar, et al., High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound, Circulation 103 (22) (2001) 2705–2710.
[3] M.S. Kim, S.J. Kang, C.H. Lee, et al., Prevalence of coronary atherosclerosis in asymptomatic healthy subjects: an intravascular ultrasound study of donor hearts, Journal of Atherosclerosis and Thrombosis 20 (5) (2013) 465–471.

[4] J.A. Kobashigawa, J.M. Tobis, J.C. Starling, et al., Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years, Journal of the American College of Cardiology 45 (9) (2005) 1532–1537.
[5] G.S. Mintz, S.E. Nissen, W.D. Anderson, et al., American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents, Journal of the American College of Cardiology 37 (2001) 1478–1492.
[6] C. Di Mario, S.H. The, S. Madretsma, et al., Detection and characterization of vascular lesions by intravascular ultrasound: an in vitro study correlated with histology, Journal of the American Society of Echocardiography 5 (1992) 135–146.
[7] H.M. Garcia-Garcia, M.A. Costa, P.W. Serruys, Imaging of coronary atherosclerosis: intravascular ultrasound, European Heart Journal 3 (2010) 2456–2469.
[8] H. Li, K. Tanaka, H. Anzai, et al., Influence of pre-existing donor atherosclerosis on the development of cardiac allograft vasculopathy and outcomes in heart transplant recipients, Journal of the American College of Cardiology 47 (2006) 2470–2476.
[9] A. Konig, E. Kilian, J. Rieber, et al., Assessment of early atherosclerosis in de novo heart transplant recipients: analysis with intravascular ultrasound-derived radiofrequency analysis, Journal of Heart and Lung Transplantation 27 (1) (2008) 26–31.
[10] S.Z. Gao, S.A. Hunt, E.L. Alderman, et al., Relation of donor age and preexisting coronary artery disease on angiography and intracoronary ultrasound to later development of accelerated allograft coronary artery disease, Journal of the American College of Cardiology 29 (1997) 623–629.
[11] C.K. Wong, A.C. Yeung, The topography of intimal thickening and associated remodeling pattern of early transplant coronary disease: influence of pre-existing donor atherosclerosis, Journal of Heart and Lung Transplantation 20 (2001) 858–864.
[12] D. Sandler, F.N. McKenzie, A.H. Melis, et al., Early death after cardiac transplantation-the role of unsuspected donor coronary artery disease, Journal of Heart and Lung Transplantation 10 (1991) 172.
[13] M.R. Mehra, H.O. Ventura, D.D. Stapleton, et al., Presence of severe intimal thickening by intravascular ultrasonography predicts cardiac events in cardiac allograft vasculopathy, Journal of Heart and Lung Transplantation 14 (4) (1995) 632–639.
[14] P.R. Rickenbacher, F.J. Pinto, N.P. Lewis, et al., Prognosis importance of intimal thickness as measured by intracoronary ultrasound after cardiac transplantation, Circulation 92 (12) (1995) 3445–3452.
[15] M.R. Mehra, H.O. Ventura, P.A. Uber, et al., Is all intimal proliferation created equal in cardiac allograft vasculopathy? The quantity–quality paradox, Journal of Heart and Lung Transplantation 22 (2) (2003) 118–123.
[16] S.R. Kapadia, S.E. Nissen, E.M. Tuzcu, Impact of intravascular ultrasound in understanding transplant coronary artery disease, Current Opinion in Cardiology 14 (2) (1999) 140–150.
[17] M. Yamasaki, R. Sakurai, A. Hirohata, et al., Impact of donor-transmitted atherosclerosis on early cardiac allograft vasculopathy: new findings by free-dimensional intravascular ultrasound analysis, Transplantation 91 (2011) 1406–1411.
[18] F.M. Sacks, M.A. Pfeffer, L.A. Moye, et al., The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators, The New England Journal of Medicine 335 (1996) 1001–1009.
[19] R. Nakazato, H. Gransar, D.S. Berman, et al., Statins use and coronary artery plaque composition: results from the International Multicenter CONFIRM Registry, Atherosclerosis 225 (1) (2012) 148–153.
[20] F. Sonntag, J.R. Schaefer, A.K. Gitt, et al., Lipid therapy in daily routine, Deutsche Medizinische Wochenschrift 137 (40) (2012) 2047–2052.
[21] A. Keogh, L. Simons, P. Spratt, et al., Hyperlipidemia after heart transplantation, Journal of Heart Transplantation 7 (1988) 171–175.
[22] B. Skalicka, M. Kubanek, I. Malek, et al., Conversion to tacrolimus and atorvastatin in cyclosporine-treated heart transplant recipients with dyslipidemia refractory to fluvastatin, Journal of Heart and Lung Transplantation 28 (6) (2009) 598–604.
[23] M. Zakliczynski, J. Boguslawska, E. Wojniak, et al., In the era of the universal use of statins dyslipidemia's are still common in heart transplant recipients: a cross-sectional study, Transplantion Proceedings 43 (8) (2011) 3071–3073.
[24] A.W. Wu, C.H.M. Ballantyne, B.C. Short, et al., Statin use and risks of death or fatal rejection in the Heart transplant lipid registry, American Journal of Cardiology 95 (2005) 367–372.
[25] K. Wenke, B. Meiser, J. Thiery, et al., Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four-year randomized trial, Circulation 96 (1997) 1398–1402.
[26] M.R. Mehra, H.O. Ventura, F.W. Smart, et al., An intravascular ultrasound study of the influence of angiotensin-converting enzyme inhibitors and calcium entry blockers on the development of cardiac allograft vasculopathy, The American Journal of Cardiology 75 (12) (1995) 853–854.
[27] E. Raichlin, S.S. Kushwaha, Proliferation signal inhibitors and cardiac allograft vasculopathy, Current Opinion in Organ Transplantation 13 (5) (2008) 543–550.
[28] S. Arora, T. Ueland, B. Wennerblom, et al., Effect of everolimus introduction on cardiac allograft vasculopathy—results of a randomized, multicenter trial, Transplantation 92 (2) (2011) 235–243.
[29] N.K. Chou, C.F. Jan, N.H. Chi, et al., Cardiac allograft vasculopathy compared by intravascular ultrasound sonography: everolimus to mycophenolate mofetil—one single-center experience, Transplant Proceedings 44 (4) (2012) 897–899.
[30] J.F. Delgado, N. Manito, J. Segovia, et al., The use of proliferation signal inhibitors in the prevention and treatment of allograft vasculopathy in heart transplantation, Transplantation Reviews (Orlando) 23 (2) (2009) 69–79.